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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	12

DATE MAILED: 05/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/801,164	BISCHOFBERGER ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

Pursuant to the directives of paper No. 10 (filed 3/25/03), claim 52 has been amended. Claim 52 remains pending. Applicants' arguments filed 3/25/03 have been considered and found persuasive in part. The previously imposed §112, second paragraph rejection is withdrawn. However, the §112, first paragraph rejection remains.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 52 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As indicated previously, there is no evidence that any of the claimed compounds exhibit antiviral activity. It is asserted (response filed 7/31/02) that the claimed compounds are prodrugs of lamivudine. However, one cannot predict, based only on a viewing of the structure of a compound, the propensity of the compound to act as a "prodrug". As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue

experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. The state of the art is such that when one takes an established drug, and modifies its structure in an effort to obtain a prodrug, "unpredictable" results are obtained. Consider the following:

- Shabat D (*Proceedings of the National Academy of Sciences* **98** (13) 7528-33, 2001) discloses a prodrug that is not activated by endogenous enzymes. This supports the conclusion of "unpredictability" in that the instantly claimed compounds may not be activated by endogenous enzymes.

- Smal (*Biochemical Pharmacology* **49** (4) 567-74, 1995) discloses (e.g., p. 572) that 2-Leu-MTX is unsuitable as a prodrug

- Saboulard (*Molecular Pharmacology* **56** (4) 693-704, 1999) discloses (e.g., page 701, col 1) that prodrugs of AZT are not effective.

- Jaffar (*Bioorganic and Medicinal Chemistry Letters* **9** (1) 113-8, 1999) discloses (e.g., table 1) prodrugs of aspirin that are not effective.

- Miyauchi M (*Chemical and Pharmaceutical Bulletin* **38** (7) 1906-10, 1990) discloses an attempt to produce orally bioavailable prodrugs of 3-thiazoliomethyl cephalosporin (compound number 1) Lipophilicity of the resulting derivatives (8-10) was suitable for passive absorption from the intestinal tract, and chemical stability in phosphate buffer solution (pH 6.86) was moderate. However, when administered orally to mice, these derivatives were mainly transformed to a novel 3-spiro cephalosporin 11, and desired reconversion to the 3-thiazoliomethyl cephalosporin was minor. These results showed that the derivatives (8-10) tested in this study did not serve as orally active prodrugs of 3-thiazoliomethyl cephalosporin 1.

- Hadad S (*Journal of Pharmaceutical Sciences*, **81** (10) 1047-50, 1992) examined the pharmacokinetics and efficacy of five monoester prodrugs of valproic acid (VPA).

Valproic acid an anti-epileptic drug. Four of the five prodrugs were ineffective in mitigating symptoms of epilepsy. In addition, a pharmacokinetic- pharmacodynamic correlation was absent in the case of B-VPA and H-VPA.

- Langer (*J. Med. Chem.* **44**, 1341-1348 2001) has examined the effects of bonding a peptide, via a linker, to daunorubicin and doxorubicin. As stated (p. 1344, col 1, paragraph 3, attaching a peptide to the amino group of daunorubicin or doxorubicin eliminated activity.

- Mamber S. W. (*Journal of Pharmacology and Experimental Therapeutics* **274** (2) 877-883, 1995) discloses prodrugs of taxol. The 2'- and 7- phosphate analogs BMY46366 and BMY46489 were ineffective as prodrugs.

- Niemi (*J. Med. Chem.* **42**, 5053, 1999) prepared compounds which were intended to be prodrugs of clodronic acid. As it happened, benzoyloxyproyl esters of clodronic acid were ineffective as prodrugs.

In response to Shabat (*Proceedings of the National Academy of Sciences* **98** (13) 7528-33, 2001), it is argued (response filed 3/25/03), that the objective of Shabat was to design a prodrug which would fail to treat cancer in animals. However, this is not true. The objective of Shabat was to succeed in treating cancer. Furthermore, Shabat applied to the label "prodrug" to the compound which was ineffective in the absence of antibody. The fact that the antibody was withheld in one experiment did not change the status of the compound as a "prodrug". At a minimum, this reference supports the conclusion that if a skilled artisan applies the label "prodrug" to a compound, such a label does not permit one to "predict" therapeutic efficacy.

In response to Miyauchi M (*Chemical and Pharmaceutical Bulletin* **38** (7) 1906-10,

1990) it is conceded (response filed 3/25/03) that attempts to create effective prodrugs of cephalosporins were not successful. However, the findings of Miyauchi are essentially dismissed as an anomaly; it is argued that it is a "general rule" that if one prepares an ester of a cephalosporin, the result will be an effective prodrug. No authority is cited for this conclusion, but in any case, Miyauchi does support a conclusion that one cannot predict the propensity of compound to liberate an active drug, merely by viewing the structure of the compound.

In response to Smal (*Biochemical Pharmacology* **49** (4) 567-74, 1995) it is argued (response filed 3/25/03) that the fact that some prodrugs were hydrolyzed more rapidly than others merely creates a choice for the skilled artisan rather than an impediment. However, by Smal's own admission, 2-Leu-MTX is unsuitable as a prodrug. If a compound liberates a "drug" but the circumstances are such that that drug is ineffective, then this reference still supports the conclusion that one cannot predict suitability and efficacy of compounds designated as prodrugs merely be viewing their structure.

In response to Saboulard (*Molecular Pharmacology* **56** (4) 693-704, 1999) it is argued (response filed 3/25/03) many of the disclosed compounds were active as prodrugs. However, not all of the disclosed compounds were active. For example compound 8 was not effective. This could not have been predicted in advance of experimentation.

In response to Jaffar (*Bioorganic and Medicinal Chemistry Letters* **9** (1) 113-8, 1999) it

is argued (response filed 3/25/03) that while it is true that some of the disclosed prodrugs were inactive, this does not "place a cloud over" prodrugs. It is not clear exactly what is meant by this. It is recognized by the examiner that there exist compounds which are effective as prodrugs. No reference of record argues to the contrary. But the issue is whether one can predict the propensity of a compound to act as a prodrug, merely upon viewing the structure of that compound. Jaffar provides strong support to the proposition that such propensity is not predictable. It is also argued (response filed 3/25/03) that a skilled artisan in possession of the Jaffar data would not have had to undergo the expenditure of "undue experimentation" in order to choose a compound that is effective as a prodrug of aspirin. This particular point is actually correct. A skilled pharmacologist, upon being presented with a listed of active compounds and a list of inactive compounds, would have had no difficulty selecting the active ones. But the question is, could the skilled artisan have predicted, in advance of experimentation, which of the compounds disclosed in Jaffar would have been effective as prodrugs? There is no evidence of record to indicate that this is the case.

In response to Langer (*J. Med. Chem.* **44**, 1341-1348 2001) it is admitted (response filed 3/25/03) that at least two of the disclosed prodrugs were inactive. It is argued, however, that several additional compounds were active, and that if the skilled artisan had been presented with the exact compounds on which data were presented, "undue experimentation"

would not have been required. But one question that arises from this analysis is, if a skilled biochemist had been presented with the compounds which were inactive, could that biochemist have achieved efficacy, absent undue experimentation? The more important point is that this reference clearly supports the examiner's position that one cannot predict the efficacy of a compound which has been labeled a prodrug, merely by viewing its structure.

In response to each of Niemi (*J. Med. Chem.* **42**, 5053, 1999) and Mamber (*Journal of Pharmacology and Experimental Therapeutics* **274** (2) 877-883, 1995) it is conceded that several inactive compounds are disclosed. But it is argued that about 50% of the tested compounds were active as prodrugs, and that for a biochemist presented with the specific compounds disclosed in Niemi or Mamber, "undue experimentation" would not have been required. However, it is the position of the examiner that if the skilled biochemist had been presented with only the inactive compounds, "undue experimentation" would have been required; more importantly, these references support the conclusion that a skilled biochemist or pharmacologist could not have predicted, in advance of experimentation, which of the compounds would have been active.

In the response filed 3/25/03, the Wands case is briefly discussed (*In re Wands* (8 USPQ2d 1400). It is observed that Wands was able to obtain IgM antibodies exhibiting the requisite 10^9 M^{-1} binding affinity constant in about 44% of the tested hybridomas. It is then implied (response filed 3/25/03) that if an applicant can demonstrate a 44% "success" rate,

following the guidance in the specification, this is sufficient to enable the claimed invention. However, applicants have not demonstrated that 44% of the compounds falling within the scope of claim 52 are converted, under physiologically relevant conditions, to lamivudine, or to another active antiviral agent (consistent with assertions in the specification). It is entirely possible that none of the claimed compounds is active as a prodrug of an antiviral agent. It is also possible that some of the claimed compounds are active. For the case of R^{34} representing a hydrogen atom, it is conceivable that the methylene group bearing phosphorous could undergo hydroxylation by a cytochrome P-450 isozyme, and that the resulting compound would hydrolyze to lamivudine, or that the hydroxyl group thus generated could be oxidized to an oxo group by another enzyme, and then the resulting compound might be vulnerable to hydrolysis by an esterase enzyme. However, there does not appear to be any mention of P-450 or any other monooxygenase; moreover, if a monooxygenase is going to be required for "liberation" of the active agent, the fact is that there are other sites in the molecule which are at least as vulnerable to oxidation as the methylene group bearing phosphorous. Oxidation at other sites (in the molecule) will result in the formation of compounds other than lamivudine. Whether formation of lamivudine is actually possible or not (under physiological conditions), the point is that one cannot predict which of the compounds will be active, and by extension, what percentage (if any) of the claimed genus will be active.

It is also argued (response filed 3/25/03) the disclosure is adequate to support the asserted utility. However, no rejection for lack of utility has been imposed by the examiner.

It is also argued that assays are disclosed in the specification on pages 64 and 107-108. On page 64, there is a general proposal, largely conceptual in nature, which can be used for compounds that contain amino acids and peptide bonds. However, most of the claimed compounds do not contain amino acids or peptide bonds. In addition, the only enzymes mentioned (on page 64) are esterases and carboxypeptidases. Even if one were to add phosphatase enzymes to the list (which has not been done on page 64), the "target" compound would still not be generated. What is required is cleavage of the CH_2/ O bond in the following structure: $(RO)_2P(=O)CH_2$-O- . There is no precedent for this occurring by an esterase or a carboxypeptidase, or even a phosphatase. Accordingly, the skilled artisan would not have found useful guidance from the information presented on page 64. On pages 107-108, an *in vitro* anti-viral assay is described for compounds other than those claimed. It is not at all clear that this assay is intended for the claimed compounds, especially since the claimed compounds are not antiviral agents *per se.* Instead, the claimed compounds have been asserted to undergo transformation to antiviral agents by the action of biochemical agents which have not yet been identified. Thus, as prodrugs, one would not have expected the claimed compounds to necessarily produce a positive result in an antiviral assay. It is also noted that on page 109, line 12+, it is asserted that the ester

groups of certain PMEA derivatives were hydrolyzed. However, these are different compounds, and moreover, the functional group which was hydrolyzed is not the same as would be required for activation of the claimed compounds.

In the response filed 3/25/03, it is suggested that the examiner comment on the various "Forman Factors" in addition to that of "unpredictability". The nature of the invention is that of compounds which are asserted to be prodrugs. It has been asserted (response filed 7/31/02) that the claimed compounds are prodrugs of lamivudine. The state of the art is such that derivatives of various pharmacologically active agents have been prepared, and in some cases, these derivatives have undergone conversion *in vivo* to compounds which had previously been demonstrated to be "drugs"; hence such derivatives have been termed "prodrugs". But the state of the art has not advanced to the point where the structural requirements that must be present in a "prodrug" can be predicted. Examples of compounds which are derivatives of known drugs, and which are not converted to the drugs *in vivo* have been given above. As for lamivudine, there is no evidence of record that prodrugs of this compound have been prepared or tested (in the prior art). As for "working examples", there are none that have direct bearing on the claimed invention. Some data is presented in the specification, but that data is for compounds which are not now being claimed. As for the the level of skill of a researcher who would endeavor to discover which of the claimed compounds (if any) will "liberate" limivudine, expertise in

organic synthesis would be required in order to obtain the compounds. In addition, expertise in organic analytical chemistry would be required to determine whether or not the limivudine had been produced under a given assay condition, and if produced, whether this compound can be produced in an amount which is pharmacologically relevant. Expertise in biochemistry and/or virology would be required to determine conditions under which limivudine is liberated, assuming that such conditions exist. As for the "breadth of the claims", it is observed that the scope is not "unduly" broad. As for the matter of guidance, there is none. As indicated above, on page 64, there is a general proposal, largely conceptual in nature, which can be used for compounds that contain amino acids and peptide bonds. However, most of the claimed compounds do not contain amino acids or peptide bonds. There is also no suggestion as to what biochemical entity might effect the requisite transformation, even for the case of R^{34} representing hydrogen. For the case of R^{34} representing a substituent other than hydrogen, there is no suggestion anywhere in the specification or in subsequent arguments as to how this R^{34} group might be removed by a biochemically relevant process. Accordingly, the skilled artisan would not have found any useful guidance from the information presented on page 64. An assay for antiviral activity is presented on page 107, but there is no indication that this is intended for any of the claimed compounds, moreover, if the claimed compounds are indeed prodrugs, the skilled artisan would not expect them to exhibit antiviral activity prior to conversion to the active

agent. Furthermore, the specification does not disclose which biochemical agent(s) might effect a transformation from the claimed compounds to lamivudine.

In accordance with the foregoing, there is no guidance in the specification (pursuant to 35 USC §112, first paragraph) as to how to use the claimed compounds to inhibit virus replication, or even how to convert the claimed compounds into a compound which will inhibit virus replication. There are no working examples which show the skilled artisan how to use the claimed compounds. There is also nothing in the prior art to show the skilled artisan how to use the claimed compounds. And as discussed at some length above, the art is very unpredictable, i.e., one cannot merely view the structure of a compound on paper, and determine on that basis its propensity to undergo conversion in vivo to a compound which will exhibit antiviral activity. Accordingly, "undue experimentation" would be required to practice the claimed invention.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE

PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

D. Lukton 5/14/03

Christopher S. F. Low

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